REMARKS

Entry of the amendment and reconsideration of the rejection of the claims in view of the following Remarks is respectfully requested.

Claims 1 and 14 have been amended. Support for the amendment can be found throughout the specification, including in original claim 4. Claim 4 has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject of this claim in a continuation application. Claim 21 has been added. The new claim is supported throughout the specification, including at page 6, lines 6-12. Claims 3, 5-7, 9, 11-13, 16-17, and 20 were withdrawn from consideration. Therefore, claims 1-3, and 5-21 are pending in the application.

Restriction

This application was subjected to a restriction requirement. Applicants previously elected Group II with traverse. Applicants now acknowledge the Examiner's decision to rejoin Groups II and VIII in the present case.

Priority

The Examiner stated that reference must be made to Application No. 60/163,132 if Applicants intend to rely on the filing date of this application for priority purposes. Applicants have submitted with this response an Application Data Sheet making reference to this Application.

Information Disclosure Statement

The Examiner noted that the references cited in the Search Report for this application will not be listed on any patent issuing from this application unless provided on a separate list in compliance with 37 CFR 1.98(a)1. Applicants submit herewith a Supplemental IDS citing the references cited in the Search Report.

Specification

The Examiner has requested that the trademarks MUTA-GENE®, NOS DETECT®, and IMAGEQUANT® be capitalized wherever they appear in the specification. Applicants have amended the specification to capitalize these terms. Applicants respectfully request withdrawal of the objection to the specification on this basis.

35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 4, 8, and 10 under 35 U.S.C. § 112 as allegedly non-enabled. The Examiner contends that the specification enables methods of treating hypertension, diabetes, thrombosis, angina, atherosclerosis, and heart failure, but not for any disorder associated with nitric oxide. Claim 4 has been canceled, rendering the rejection of this claim moot. Applicants respectfully traverse this rejection with respect to the other claims.

Applicants contend that one of skill in the art reading the specification would be able to make and use the methods as claimed without undue experimentation. There are many factors to be considered in an analysis of enablement including breadth of claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing In Re Wands, 858 F2d 731, 737 (Fed. Cir. 1988). Only a reasonable correlation between enablement and the scope of the claims is required.

The specification discloses that VEGF is a regulator of angiogenesis and vasculogenesis (page 1, lines 28-29). The specification also discloses that nitric oxide and endothelial NO synthase (eNOS) are involved in various VEGF-induced activities, and that nitric oxide is an important mediator of endothelial function, and a regulator of vascular homeostasis, platelet aggregation, and angiogenesis (page 4, lines 23-27). Applicants have discovered that VEGF treatment upregulates eNOS expression and activity, thereby enhancing sustained nitric oxide production (page 5, lines 42-44). The specification discloses, therefore, that VEGF or VEGF receptor agonists can be useful in the treatment of nitric oxide associated disorders. Applicants also disclose multiple examples of nitric oxide associated disorders, including hypertension, diabetes, atherosclerosis, thrombosis, angina, and heart failure (page 6, lines 6-9).

The specification, therefore, discloses multiple examples of disorders comprising the genus of nitric oxide associated disorders. Applicants submit that these examples are representative of the genus of nitric oxide associated disorders, and that there is no reason of record to the contrary. Based upon the information in the specification as discussed above, one of skill in the art would reasonably predict that Applicants' claimed methods would also be applicable to other nitric oxide associated disorders within the genus. Consequently, Applicants respectfully submit that one of skill in the art would be able to make and use Applicants' invention as claimed to treat other nitric oxide associated disorders without undue experimentation. Claims 1, 8, and 10 are therefore fully enabled, at least for the foregoing reasons, and withdrawal of the rejection is requested.

The Examiner also rejected claims 15 and 18 under 35 U.S.C. § 112 as allegedly non-enabled. The Examiner asserts that the specification does not enable any VEGF variant with substitutions between positions 63-66 that selectively bind KDR receptors. Applicants respectfully traverse this rejection.

Applicants submit that when the factors used to determine enablement as described above are carefully weighed, claims 15 and 18 are clearly enabled by the specification. Claim 15 is directed to a method of stimulating sustained production of endogenous NO in an endothelial cell by administering a VEGF variant receptor agonist. Claim 18 further recites that the variant comprises one or more amino acid substitutions at or between positions 63 to 66 of the native VEGF sequence.

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient [to enable the claims] if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." MPEP 2164.02. Applicants submit that the present specification provides representative examples that are clearly sufficient to enable the full scope of these claims.

Applicants have provided working examples for a method of producing VEGF variants, and selecting for variants displaying selectivity for the KDR receptor (Examples 6 and 7). Using this method, Applicants obtained and disclosed twenty-nine different variants having KDR selectivity (Table 2). The specification further discloses in Table 2 the precise nature of the differences in amino acid sequence between native VEGF and the variants. Applicants submit, therefore, that the specification provides representative examples of the claimed genus such that the genus is fully enabled.

The Examiner acknowledges that the specification enables several KDR-selective VEGF variants wherein the variants have substitutions of serine at residue 63 serine; methionine or alanine at residue 65; and arginine or threonine at residue 66. However, the Examiner asserts that the disclosure provides no other examples of VEGF variants having selectivity for KDR. Applicants respectfully disagree. As stated above, Applicants have disclosed 29 different examples of VEGF variants displaying KDR selectivity. Applicants have also provided guidance as to which positions can be substituted and provided guidance as to the type of substitutions. (See the specification at page 14; Table 1) Applicants submit it would be routine experimentation for one of skill in the art to determine which substitutions can be made at those positions and have KDR selectivity. Therefore, Applicants have in fact disclosed multiple examples of variants other than those specifically recited in claim 18.

Based on the foregoing, Applicants submit that the large number of variants identified in the specification are representative of the claimed genus. Applicants further submit that one of skill in the art would expect from these representative variants that the claimed genus could be used without undue experimentation, such that the claims are fully enabled under the guidelines set forth in the MPEP as quoted above.

The Examiner contends, however, that using the claimed genus would involve undue experimentation because the predictability of which nucleotides can be deleted or inserted or substituted is extremely complex. Applicants respectfully disagree. "The fact that even complex experimentation must occur to make and use the disclosed invention does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 2164.01. Furthermore, if

the methods needed to practice an invention are well known, that fact argues against a finding of undue experimentation. MPEP 2164.01(a) (citing *In re Wands*, 858 F.2d 731) (Fed. Cir. 1988).

Applicants submit that methods for screening variants of a native protein are in fact both well-known and routine to those of skill in the art. Indeed, Applicants have provided extensive information and working examples on how to screen for VEGF variants having selectivity for the KDR receptor (Example 7). Furthermore, Table 2 discloses the amino acid residue differences between each variant and native VEGF. The nature and position of the amino acid sequence differences possessed by the large number of disclosed variants, relative to native VEGF, provides extensive guidance to one of skill in the art as to what amino acid positions one may wish to select first for mutation, in order to maximize the chances of successfully obtaining VEGF variants selective for the KDR receptor. Furthermore, Applicants have provided further guidance in Table 1 as to what substitutions may be desirable to make for a given amino acid. Finally, Applicants have disclosed the amino acid residues of native VEGF found to play a predominant role in binding KDR and FLT-1 receptors (page 4, lines 1-7).

Therefore, Applicants' disclosure of a large number of VEGF variants, and of the location of the KDR and FLT-1- binding regions of native VEGF, provides significant disclosure and guidance concerning the correlation between the primary amino acid structure of VEGF and its relative affinity for the KDR receptor. Armed with this information, along with the information of the art, one of skill in the art could readily obtain additional VEGF variants selective for the KDR receptor. Since those of skill in the art routinely engage in this type of experimentation, as discussed above, Applicants submit that the experimentation required to practice the full scope of the claimed invention is not undue.

Applicants submit that claims 15 and 18 are fully enabled by the specification, for at least the foregoing reasons. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 102

The Examiner rejected claims 1, 2, 8, 10 and 14 under 35 U.S.C. § 102(b) as anticipated by Martin et al. The Examiner contends that this reference discloses that VEGF stimulates nitric oxide production, and that VEGF agonists are useful in the treatment of nitric oxide conditions

such as hypertension, heart failure, and atherosclerosis. Applicants respectfully traverse this rejection.

Independent claims 1 and 14 as amended recite that the VEGF variant or VEGF receptor agonist is selective for a KDR receptor. Applicants submit that Martin et al. nowhere teach or suggest a VEGF variant or VEGF receptor agonist that is selective for a KDR receptor. A KDR selective agonist is beneficial because native VEGF has multiple biological effects and may cause unwanted adverse effects (page 12, lines 36-42). Martin et al. nowhere teaches or suggests the significance or desirability of obtaining a KDR-selective VEGF receptor agonist. Applicants submit, therefore, that claim 1 and its dependent claims 2, 8, and 10 and claim 14 are patentable over Martin et al. at least for this reason. Withdrawal of the rejection is therefore requested.

The Examiner rejected claims 1, 2, 4, 8, 10, 14, 15, and 18 under 35 U.S.C. § 102(a) and (e) as anticipated by Keyt et al. The Examiner contends that this reference teaches KDR-selective VEGF variants having mutations spanning amino acid residues 63-67. Claim 4 has been cancelled. With respect to the remaining claims, Applicants traverse this rejection.

Applicants submit that this reference is not properly considered prior art under 35 U. S. C. 102(a). Applicants submit the Keyt patent published after our earliest effective filing date of November 2, 1999. Applicants submit an application data sheet to perfect the claim for priority. Applicants respectfully request withdrawal of the rejection on this basis.

With respect to the 102 (e) rejection, Applicants submit that the Examiner has not shown where the Keyt et al. reference teaches administering VEGF variants or VEGF receptor agonists that are selective for a KDR receptor to treat a nitric oxide associated disorder, or to stimulate sustained production of endogenous NO in an endothelial cell. In addition, the Examiner has not shown where the cited reference teaches that agonists or variants displaying selectivity for the KDR receptor should be selected over a non-KDR selective agonist or variant for use in the treatment of a nitric oxide associated disorder. Applicants respectfully submit that claim 1 and claim 14 and dependent claims 2, 8, 10, 15, and 18 are patentable over Keyt et al.at least for these reasons. Withdrawal of the rejection is therefore requested.

35 U.S.C. § 103(a) and 103(e)

Claims 1, 2, 4, 8, 10, 14, 15, 18, and 19 were rejected under 35 U.S.C. 103(a) as unpatentable over Keyt et al. Applicants traverse this rejection.

Applicants submit that the Keyt patent is not properly considered prior art under 102(a) or 102 (e). Under 102 (a), applicants submit the Keyt patent published after our earliest effective filing date of November 2, 1999. Applicants submit an application data sheet to perfect the claim for priority.

Applicants submit that the Keyt et al patent, Patent No. 6,022,473 is not properly considered prior art under 35 U. S. C. 102 (e). The Keyt et al. reference is a U.S. patent with a filing date of December 5, 1995 and an issue date of Feb. 1, 2000. It appears that the Examiner has considered this reference prior art under § 102(e).

A reference that is prior art only under § 102(e) cannot be used, according to § 103(c), in an obviousness rejection if the subject matter of the cited reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. A clear statement of entitlement to the prior art exclusion by Applicants or a registered practitioner is a sufficient evidence to establish the prior art exclusion (Examination Guidelines for 35 U.S.C. § 102(e) (as amended and revised) at IV(5); 1266 TMOG 80, January 14, 2003).

Applicants hereby make a clear statement of entitlement to exclude the Keyt et al. reference as prior art as provided by § 103(c). The Keyt et al. patent is assigned to the assignee of the present patent application. The Keyt et al. patent and the present patent application were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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